ATTACHMENT 3

FDA GUIDANCE

11/23/99

Guidance for Industry

Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products

Additional copies of this guidance document are available from Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm

For questions regarding this document, contact the Director, Division of Hematology, at 301-496-4396.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
November 1999

TABLE OF CONTENTS

NOTE: Page numbering can vary in documents distributed electronically.

GUIDANCE FOR INDUSTRY[1]

Revised Precautionary Measures To Reduce The Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products

I. INTRODUCTION

On August 17, 1999, the Food and Drug Administration (FDA) issued a guidance document entitled, "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products." FDA issued the guidance for immediate implementation, and requested that comments on the guidance document be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the guidance.

After reviewing the comments received, FDA has revised the August 1999 guidance by issuing this document. This guidance provides comprehensive current recommendations, including new recommendations concerning nvCJD. This guidance is released for immediate implementation. FDA interprets immediate implementation to mean as soon as feasible, but not later than April 17, 2000.

FDA recognizes that the scientific technology for determining individuals at risk for CJD and nvCJD, and detecting the infectious agents in tissues and in products, is continuing to advance, and that there may be a need for future updating of the relevant guidance.

II. BACKGROUND

CJD is a rare but invariably fatal degenerative disease associated with a poorly understood transmissible agent (1, 2). CJD cases occur at low frequency by an unknown mechanism (sporadic CJD). It may also be acquired by exogenous (usually iatrogenic) exposure to infectious material; or may be familial, caused by a genetic mutation of the prion protein gene. Clinical latency for iatrogenic CJD may exceed 30 years.

---

[1] This guidance document represents the agency's current thinking on precautionary measures to reduce the possible risk of transmission of Creutzfeldt-Jakob Disease (CJD) and new variant CJD (nvCJD) by blood and blood products and to assure that blood and blood products are not adulterated or misbranded, within the meaning of the Federal Food Drug and Cosmetic Act, and are safe, pure and potent within the meaning of the Public Health Service Act. It does not create or confer any rights for or on any person and does no operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

In 1996, a previously unrecognized variant of CJD was described almost exclusively in the United Kingdom (3), and is referred to as new variant CJD (nvCJD). Although to date only 48 patients have died of nvCJD, the extent of a nvCJD epidemic in the United Kingdom cannot yet be determined. No cases of nvCJD have been identified in the United States. Laboratory and epidemiologic studies have linked nvCJD to an outbreak of bovine spongiform encephalopathy (BSE) in the United Kingdom (4, 5). BSE infection in cattle appeared in 1980, peaked in 1992, and fell to low levels by 1996.

On December 11, 1996, FDA issued a Memorandum to all registered blood and plasma establishments and all establishments engaged in manufacturing plasma derivatives entitled "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products." The memorandum recommended as a precaution, to quarantine and destroy in-date Source Plasma and plasma derivatives, and in-date transfusion products prepared from donors who were at increased risk for developing CJD or who were subsequently diagnosed with CJD. The memorandum recommended permanent deferral of donors with CJD or CJD risks, unless, for cases of genetic risk, the donor underwent genetic testing which did not reveal a familial-CJD associated abnormality of the prion protein gene. This document did not make recommendations specific to nvCJD. New FDA recommendations announced on September 8, 1998, specified: 1) reversal of the recommendation to withdraw plasma derivatives from donors with classic CJD or CJD risk factors; and 2) recommendation to withdraw all material from nvCJD donors. These recommendations were incorporated into a guidance published on August 17, 1999 entitled "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products," which is replaced by this guidance. This document contains changes and clarifications undertaken as a result of comments to the August 1999 publication.

A. CJD: Rationale for Not Withdrawing Plasma Derivatives from Donors with CJD or CJD Risk

Accumulating epidemiologic information and laboratory studies have indicated that transmission of the CJD infectious agent by blood products is highly unlikely. Five published case-control studies analyzed over 600 CJD cases. None of these studies showed that blood transfusion increased the risk for CJD (6-8). Investigations of recipients of blood components from known CJD donors have not revealed transmission of the CJD agent (9, 10), although these cohort studies are limited by the small numbers of such recipients, especially with long-term follow-up, and thus would only be likely to reveal a high transmission rate. National mortality surveillance performed by the Centers for Disease Control and Prevention (CDC) indicates that patient populations with increased exposure to blood or blood products are not at increased risk for CJD (11). During a 18-year period (1979-96), 4,468 cases of CJD were reported to CDC. When death records were searched, none of these cases were

reported to have had hemophilia, thalassemia, or sickle cell disease. More directed evaluation of persons with hemophilia have not shown a link to CJD. In one study, brain tissue from 24 hemophiliacs who died with neurologic disease was examined; none had evidence of CJD (12). In a second study, brain tissue from 33 hemophiliacs in the United Kingdom, who died of various causes was examined, and none had evidence for CJD (13). Additional surveillance of cryoprecipitate recipients is underway in Seattle, WA. Through 1997, no CJD cases have been reported among 101 patients who, together, received over 238,000 units of cryoprecipitate between 1979-85; 76 of these subjects are alive from 12.5 to 18.5 years later (14). Three of these recipients were known to have received at least one unit of cryoprecipitate from donors known to have developed CJD.

While epidemiological studies have not revealed transmission of CJD in humans by blood and blood products, and laboratory experiments have demonstrated that manufacturing significantly lowers the amount of the CJD infectious agent in plasma derivatives, some laboratory experiments have shown that blood and plasma fractions from experimentally infected animals transmit CJD to recipient animals when directly injected into the brain (15-17). In two cases, transfusion of blood directly from an infected hamster transmitted disease to the recipient (Transmissible Spongiform Encephalopathy (TSE) Advisory Committee transcript, December 1998; Paul Brown, personal communication) (26).

In contrast, other laboratory studies have not supported the transmission of CJD through transfusion of blood. Transfusion of blood units from 3 CJD patients failed to transmit CJD to chimpanzees (15), and the validity of reported positive transmissions to animals using blood from patients with CJD has been questioned (17).

Plasma derivatives are unlikely to transmit disease in humans because: 1) a CJD-implicated plasma unit would be diluted into a large plasma pool, leading to a low number of infectious units in a dose of the final product, 2) intravenous and intramuscular inoculation alone is less efficient than cerebral inoculation for CJD transmission, and 3) further processing of plasma pools by Cohn fractionation and manufacturing processes such as column chromatography, precipitation, and filtration, have been shown to diminish titers of CJD-like agents, in spiking experiments using scaled-down manufacturing procedures (16, 25) (FDA TSE Workshop, September 13-14, 1999).

B. NvCJD: Current Case Definitions, and Rationale for Withdrawing Plasma Derivatives From Donors with NvCJD

NvCJD is distinguished from CJD by differences in clinical presentation and neuropathologic changes (3, 18-20). Clinically, nvCJD patients have an earlier age of onset, with mean age at death of 29 years, compared to CJD patients, whose mean age

at death is 67 years. NvCJD presents with predominantly psychiatric and sensory symptoms, and absence of diagnostic EEG changes frequently seen in CJD. NvCJD patients have a more prolonged duration of illness (median survival 14 months) than patients with CJD (median survival 4 months) (21). Neuropathologic features of nvCJD include florid prion protein plaques surrounded by spongiform changes, which are rarely found in CJD. In addition, prion protein can be detected immunohistochemically in the lymphoid tissues of nvCJD, but not CJD patients (22). This observation led to concerns that transmission of nvCJD by blood might be possible.

Neuropathologic examination of brain tissue is required to confirm a diagnosis of nvCJD. A confirmed or definite case of nvCJD is currently defined by the following neuropathologic findings: 1) numerous widespread kuru-type amyloid plaques, surrounded by vacuoles, in both cerebellum and cerebrum ("florid plaques"); 2) spongiform change most evident in the basal ganglia and thalamus, with sparse distribution in the cerebral cortex; and 3) high density accumulation of prion protein, particularly in the cerebrum and cerebellum as shown by immunohistochemistry.

In cases where adequate neuropathology specimens are not available, a clinical diagnosis of "suspected" nvCJD could be made based upon certain atypical clinical features. Although recommended diagnostic evaluations and criteria for nvCJD are evolving, at present the CDC would classify cases in the United States with all of the following features as "suspected" nvCJD:

1. Current age (if alive) or age at death <55.
2. Persistent painful sensory symptoms and/or psychiatric symptoms at clinical presentation.
3. Dementia, and delayed development (≥4 months after illness onset) of ataxia, plus at least one of the following three neurologic signs: myoclonus, chorea, or dystonia.
4. A normal or abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.
5. Duration of illness greater than 6 months.
6. Routine investigations do not suggest an alternative, non-CJD diagnosis.
7. A history of possible exposure to bovine spongiform encephalopathy (BSE), e.g., having been a resident or traveler to a BSE-affected country from 1980 through 1996.
8. No history of iatrogenic exposure to CJD, such as receipt of a dura mater graft, or human pituitary-derived hormones.
9. The patient does not have a prion protein gene mutation, or, if this has not been determined, there is no history of CJD in a first degree relative.

The transmissibility of nvCJD by blood or blood products is unknown, although laboratory and epidemiologic studies are underway to evaluate this risk. NvCJD appears to be distinct from classic variants of CJD both clinically and biologically and therefore transmissibility cannot confidently be predicted from studies of CJD. Until more is known about the possibility of nvCJD transmission by blood components or plasma derivatives, a precautionary policy of withdrawal for all of these products is recommended for material from donors with nvCJD.

C. Current CJD and NvCJD Recommendations

On January 29, 1998, the Public Health Service (PHS) Advisory Committee on Blood Safety and Availability reviewed laboratory and epidemiologic information concerning CJD transmissibility by blood, as well as the impact of CJD-related withdrawals upon the supply of medically necessary plasma derivatives. Based upon this review, the committee recommended that FDA consider revising its December 11, 1996 guidance to the extent necessary to relieve shortages of medically necessary plasma derivatives. Subsequently, epidemiological and laboratory studies were evaluated by the Department of Health and Human Services Blood Safety Committee, which determined at its July 23, 1998 meeting, that the current CJD guidance on quarantine and withdrawal of blood products should be revised. A policy position to modify the withdrawal recommendations for plasma derivatives was announced by Surgeon General David Satcher, M.D. on August 27, 1998, at a public meeting of the PHS Advisory Committee on Blood Safety and Availability. It was recommended that plasma derivatives be withdrawn and intermediates quarantined only if a blood donor develops nvCJD and that previously recommended withdrawals and quarantines be discontinued for classical CJD and CJD risk factors. A consistent recommendation was made available on the Internet by the FDA on September 8, 1998.

United Kingdom residents have an increased risk of developing nvCJD. The number of people incubating nvCJD in the United Kingdom cannot yet be predicted. The FDA received additional advice from the TSE Advisory Committee (25) on December 18, 1998, concerning deferral of donors who have traveled to or resided in the United Kingdom for a certain period of time, and therefore could have been exposed to the nvCJD agent. The TSE Advisory Committee recommended deferring such donors, but requested additional information concerning the impact of deferrals on the blood supply in order to provide more specific advice about time of residence in the United Kingdom. On June 2, 1999, the TSE Advisory Committee reaffirmed its recommendation to defer donors who have traveled to or resided in the United Kingdom, until more is known about the potential risk of nvCJD incubation in such donors and about the ability of blood to transmit nvCJD (26).

Comprehensive revised recommendations based upon the above discussions and PHS and FDA internal deliberations are contained in this guidance document.

Recommendations for donor deferral, product retrieval, quarantine, and disposition, and recipient tracing and notification have been developed based upon consideration of risk in the donor, risk in the product, and the effect of withdrawals on the supply of life- and health-sustaining blood components and plasma derivatives. In particular, nvCJD is distinguished from CJD and CJD risk factors, based on lack of sufficient historical and epidemiological experience, and lack of available scientific studies relevant to the likelihood of transmission of nvCJD via blood components or derivatives.

III. RECOMMENDATIONS FOR DONOR DEFERRAL

A. Recommended Donor Deferral Criteria

1. FDA recommends that donors who have been diagnosed with nvCJD or CJD be permanently deferred.

2. FDA recommends that donors at increased risk for CJD (as identified by questions in section III.B.) be indefinitely deferred and appropriately counseled. Donors are considered to have an increased risk for CJD if they have received a dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives with CJD.

3. FDA believes that donors who have resided in the United Kingdom (as identified by questions in section III.D.) may be at risk for acquiring nvCJD. As a precaution, FDA recommends that donors who have spent six months or more cumulatively in the United Kingdom from 1980 through 1996 (i.e., from January 1, 1980 through December 31, 1996) be indefinitely deferred.

4. FDA recommends that donors who injected bovine insulin since 1980 be indefinitely deferred unless it has been established that the product was not manufactured since 1980 from cattle in the United Kingdom. FDA has previously recommended that material from cattle in BSE countries not be used in the manufacture of FDA regulated products (59 FR 44591, August 29, 1994). At this time, FDA recommends that donors known to have injected insulin be further questioned to exclude the possibility that they received bovine insulin since 1980.

B. Recommended Questions for Identifying Donors at an Increased Risk for CJD

FDA recommends that Source Plasma donors be questioned at the first donation and at each annual physical examination thereafter, and that Whole Blood donors be questioned at the time of each donation. If the donor is not familiar with the term

"Creutzfeldt-Jakob Disease," it may be taken as a negative response. These questions are similar to those in the December 11, 1996 guidance.

Question 1) "Have you or any of your blood relatives had Creutzfeldt-Jakob Disease or have you ever been told that your family is at an increased risk for Creutzfeldt-Jakob Disease?"
NOTE: This may be asked as one or two questions in order to elicit complete information regarding a family history of CJD.

Question 2) "Have you ever received human pituitary-derived growth hormone?"
NOTE: If the donor is uncertain about his or her treatment, the following question describing human pituitary-derived growth hormone injections may be asked: "Was the hormone treatment given repeatedly by injection?"

Question 3) "Have you received a dura mater (or brain covering) graft?" This question may be preceded by the more general, "Have you ever had brain surgery?" The specific question needs to be asked only if the donor responds in the affirmative to the general question.

FDA considers that donors who answer "Yes" to any of the above questions are at an increased risk for developing CJD.

C. Recommendations Regarding Donor Reentry After Donor Deferral for Risk of Familial CJD

If a donor is deferred because of family history (one or more family members with CJD), that donor may be reentered if:

1) The diagnosis of CJD in the family member(s) is confidently excluded, or CJD in the family member(s) is iatrogenic, or the family member(s) is(are) not a blood relative(s); or

2) Laboratory testing (gene sequencing) shows that the donor does not have mutations associated with familial CJD.

D. Recommended Questions for Identifying Donors at Risk for Exposure to BSE

Note that the United Kingdom is defined as England, Scotland, Wales, Northern Ireland, Isle of Man, and Channel Islands. Residence in the Republic of Ireland is not

counted as contributing to risk of nvCJD exposure. FDA recommends that, within an Establishment, current donors need only be questioned once and new donors questioned at the first donation only.

1. Donors who have resided or traveled to the United Kingdom

   Question 1) Have you visited or lived in the United Kingdom (England, Northern Ireland, Scotland, Wales, the Isle of Man, or the Channel Islands) from 1980 through 1996?

   Question 2) If so, have you spent a total time of 6 months or more in the United Kingdom from 1980 through 1996?

   FDA recommends that donors who answer "Yes" to both of the above questions be indefinitely deferred. These questions may be combined into a single question which contains all of the above information.

2. Donors who have been injected with bovine insulin since 1980

   No cases of transmission of nvCJD have been reported in recipients of bovine insulin or other injectable products manufactured in BSE-affected countries. However, as a precaution, FDA has recommended that material from cattle in BSE countries not be used in the manufacture of FDA regulated products (59 FR 44591, August 29, 1994). FDA is aware that some diabetic patients are importing bovine insulin for personal use. Additionally, some insulin products legally distributed in the United States since 1980 were manufactured from cattle in the United Kingdom. As a precaution, FDA recommends that blood donors who have injected bovine insulin since 1980, be indefinitely deferred unless it has been established that the product was not manufactured since 1980 from cattle in the United Kingdom.

The following question or a similar question is recommended to be asked of applicable potential donors:

Question: Have you at any time since 1980 injected bovine (beef) insulin?

Since the above question is only applicable to a subset of potential donors, FDA recommends that the question be asked as a secondary question when a donor responds to a general medication question that the donor is taking insulin.

Blood establishments should review their policies regarding acceptance of insulin dependent diabetic patients as donors and their donor history questions to determine if or at which point in the interview process the above question should be asked. If the donor answers "yes" or "don't know" to the question, FDA recommends that the donor be indefinitely deferred, unless it has been established that the product was not manufactured since 1980 from cattle in the United Kingdom.

IV. RECOMMENDATIONS FOR PRODUCT RETRIEVAL AND QUARANTINE

A. Blood Components

The recommended disposition of blood components is the same for all of the following: donors with CJD, donors with CJD risk factors, donors with nvCJD, and donors with potential exposure to nvCJD (travel or residence in the United Kingdom for 6 months or more, cumulatively from 1980 through 1996, or recipients of bovine-derived insulin since 1980 unless it has been established that the product was not manufactured since 1980 from cattle in the United Kingdom).

1. FDA recommends that all in-date blood components under the control of the Establishment (Whole Blood, blood components, Source Leukocytes, Pooled Platelets, unpooled Source Plasma) that were collected from the donor and intended for use in transfusion or for further manufacturing into injectable products be immediately retrieved and quarantined for subsequent destruction. An exception can be made for Source Plasma and recovered plasma based on knowledge that product distributed to a given consignee prior to a certain time will no longer exist in the form of unpooled units. FDA is not recommending the withdrawal and quarantine of classical CJD materials intended for further manufacturing into non-injectable products; however FDA recommends that such products be labeled appropriately (see section VI.A. for labeling recommendations). FDA recommends that material from nvCJD donors be immediately retrieved and quarantined, but may be saved for use in research on nvCJD by laboratories qualified to use this material (see section VI.A. for labeling recommendations). Furthermore, FDA recommends that Establishments immediately notify the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the Centers for Disease Control and Prevention (CDC) at (404) 639-3091, and the FDA, Director, Division of Hematology at (301) 496-4396, if they receive a report of a donor with nvCJD.

FDA also recommends immediate notification of CDC and FDA in case of a post donation report of a donor with a physician's clinical or pathological diagnosis of CJD and age less than 55 years. Donors under 55 years of age who are diagnosed with CJD will be investigated and reviewed by FDA in collaboration with CDC. The purpose of such investigations will be to assess the likelihood of nvCJD, in order to identify any case which occurs in the United States.

2. FDA recommends that all consignees should be notified within one week after receipt of post donation information, to immediately retrieve and quarantine any implicated in-date blood components intended for use in transfusion or for further manufacturing into injectable products, for subsequent destruction. NvCJD-implicated material may be saved for use in research on nvCJD by qualified laboratories (see section VI.A. for labeling recommendations).

B. Plasma Derivatives

1. Plasma derivatives from donors with CJD or CJD risk factors, or potential exposure to nvCJD (as defined in section III.A.)

   a. FDA recommends that pooled plasma, intermediates, and derivatives should not be withdrawn.

   b. FDA recommends consignee notification for all plasma intended for further manufacture into derivatives. An exception can be made for Source Plasma and recovered plasma based on knowledge that product distributed to a given consignee prior to a certain time will no longer exist in the form of unpooled units. Consignee notification is recommended in order to effect withdrawal of plasma that has not already been pooled for manufacture. FDA recommends that single, unpooled units of plasma be retrieved and quarantined for subsequent destruction. FDA does not recommend retrieval and quarantine of plasma that has been pooled prior to consignee notification.

2. Plasma derivatives from donors diagnosed with nvCJD

   FDA recommends that Establishments immediately notify the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the Centers for Disease Control and Prevention (CDC) at (404) 639-3091, and the FDA, Director, Division of Hematology at (301) 496-4396, if they receive a report of a donor with nvCJD.

a. FDA recommends that if an Establishment receives a post donation report of nvCJD diagnosis, the Establishment immediately retrieve and quarantine for subsequent destruction pooled plasma, intermediates, and derivatives, and any other materials containing plasma from the nvCJD donor. Alternatively, material from nvCJD donors may be saved for use in research on nvCJD by qualified laboratories (see section VI.A. for labeling recommendations). FDA recommends against the use of such material for non-injectable products.

b. FDA recommends that, within one week of receiving a post donation report of nvCJD diagnosis, the Establishment notify all consignees to immediately retrieve and quarantine for subsequent destruction pooled plasma, intermediates, and derivatives, and any other materials containing plasma from the nvCJD donor. Alternatively, this material may be saved for use in research on nvCJD (see section VI.A. for labeling recommendations).

3. Plasma derivatives from donors with a physician's clinical or pathological diagnosis of CJD and age less than 55 years

FDA recommends that Blood or Plasma Establishments immediately notify the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the Centers for Disease Control and Prevention (CDC) at (404) 639-3091, and the FDA, Director, Division of Hematology at (301) 496-4396, if they receive a report of a donor with a physician's clinical or pathological diagnosis of CJD and age less than 55 years.

Donors under 55 years of age who are diagnosed with CJD will be investigated and reviewed by FDA in collaboration with CDC. The purpose of such investigations will be to assess the likelihood of nvCJD, in order to consider precautionary withdrawal of plasma derivatives.

a. Recommendations to quarantine and withdraw plasma derivatives from such donors will be made by FDA on a case-by-case basis, depending upon results of the investigation. Precautionary quarantine and withdrawal may be advised if available information is ambiguous, and does not clearly eliminate the possibility of nvCJD.

b. FDA recommends that quarantined and withdrawn material from such donors should be treated in the same manner as for nvCJD (see section IV.B.2.).

C. Disposal of Retrieved and Quarantined Products

The transmissible agent of CJD is quite resistant to most disinfecting regimens. There is no current consensus of specific details of decontamination requirements for blood products. However, the preferred methods of destruction of CJD-implicated material are steam autoclaving at 132° C for 1-4 hours, incineration, or treatment with 1 N NaOH or concentrated sodium hypochlorite for at least 1 hour at room temperature (23, 24, 27). These treatments are known to diminish, but may not completely eliminate, infectivity.

FDA believes that blood components and plasma derivatives from donors with nvCJD, or which have been withdrawn because the donor might have nvCJD, may be saved for use in research on nvCJD by qualified laboratories (see section VI.A. for labeling recommendations).

V. RECOMMENDATIONS FOR RECIPIENT TRACING AND NOTIFICATION

If a donor is found to have CJD, nvCJD, risk factors for CJD (see NOTE, below) or if withdrawal is recommended in cases under investigation for nvCJD, FDA recommends that Establishments identify blood components prepared from prior collections from that donor. FDA recommends that the search of records to identify prior collections from that donor extend back no less than five years, and indefinitely to the extent that computerized electronic records are available. Following identification of prior collections, Establishments should inform all consignees (i.e., transfusion services) of previously distributed blood components from that particular donor. Consignee notification will enable the consignee to inform the physician or other qualified personnel responsible for the care of the recipient so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of care providers.

In cases of donors diagnosed with nvCJD or donors under investigation for nvCJD, FDA recommends that Establishments inform consignees of affected plasma derivatives as well as blood components.

NOTE: If a donor has a history of CJD in only one family member, or if a donor is found to have risk factors for nvCJD (due to six months domicile in the United Kingdom from 1980 through 1996, or due to injection of bovine insulin), FDA recommends consignee notification for the purpose of quarantine and disposition of in-date blood components (see section IV.A.). However, FDA does not recommend consignee notification for the purpose of tracing and notifying prior recipients.

VI. LABELING RECOMMENDATIONS

A. Labeling of Implicated Products for Research or Intended for Further Manufacture into Non-Injectable Products

FDA recommends that blood components from donors with CJD or who are at increased risk for CJD or exposure to nvCJD, intended to be used in research or manufacture into non-injectable products, be appropriately labeled with the following statements:

1. "Biohazard";

2. "Collected from a donor determined to be at risk for CJD"; or "Collected from a donor diagnosed with CJD"; or "Collected from a donor with potential risk of exposure to new variant CJD"; and

3. "For laboratory research use only"; or "Caution: for use in manufacturing non-injectable products only."

FDA believes that blood components from donors with nvCJD should not be used for further manufacture into non-injectable products. However blood components and plasma derivatives from donors with nvCJD or which have been withdrawn on a case-by-case basis for suspicion of nvCJD, may be used in laboratory research on nvCJD by qualified laboratories. FDA recommends that these products be labeled with the following statements:

1. "Biohazard";

2. "Collected from a donor with new variant CJD"; and

3. "Only for laboratory research on new variant CJD".

B. Labeling of Non-Implicated Products

No transmission of CJD or nvCJD by human blood components or plasma derivatives has been documented to date. However, as a precaution, FDA recommends that all blood components and plasma-derived products include labeling to address the theoretical risk. Because albumin has never been known to transmit viral diseases, and because laboratory experiments suggest that albumin is less likely to contain CJD-like agents than other plasma fractions, FDA believes that a more specific statement may be provided in the package insert for albumin and products containing albumin.

1. For Whole Blood and blood components, FDA recommends the Circular of Information be revised to include under "Side Effects and Hazards," the following statement:

   "Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

Until the circular is revised, this statement may be inserted or attached to the current circular.

2. For plasma-derived products other than albumin, FDA recommends the package insert warning section be revised to include the following statement:

   "Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

3. For plasma-derived albumin, FDA recommends the package insert warning section be revised to include the following statement:

   "Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin."

4. For products containing plasma-derived albumin, FDA recommends the package insert warning section be revised to include the following statement:

   "This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin."

VII. IMPLEMENTATION OF RECOMMENDATIONS

The recommendations contained in this guidance may be implemented without prior approval from the agency. FDA recommends that Establishments implement this guidance as soon as feasible, but not later than April 17, 2000. Licensed Establishments implementing these recommendations should submit in their annual reports (21 CFR 601.12(d)) a statement indicating the date that revised standard operating procedures (SOPs) consistent with the recommendations have been established and implemented. If Establishments elect to use an insert to incorporate the language recommended in this guidance (until the Circular of Information is revised), the annual report may also reference the date of use of the insert. In the event that a Blood Establishment elects to use other wording, FDA requests the Establishment to submit the labeling in accordance with 21 CFR 601.12(f)(2). FDA further requests manufacturers of plasma-derived products to submit labeling changes in accordance with 21 CFR 601.12(f)(2).

If a manufacturer of blood components or plasma-derived products believes that an alternative approach to the recommendations contained in this guidance document would provide equivalent protection, the manufacturer is invited to discuss the approach with FDA.

VIII. REFERENCES

1. Am. J. Pathol. 1995 146:785-811.
2. Ann Neurol. 1979 5:177-88.
3. Lancet 1996 347:91-5.
4. Nature 1996 383: 685-690
5. Nature 1997 389: 498-501
6. Neurol. 1996 46:1287-91.
7. Lancet 1993 341:205-7.
8. Lancet 1998 351:1081-5.
9. Lancet 1994 343:298-9.
10. Transfusion 1997 37(suppl.):2S.
11. Emerging Inf. Diseases 1997 2(4):333-36.
12. Transfusion 1998 38:817-20.
13. Thromb. Haemost. 1998 80:909-11.
14. A. Thompson, unpublished.
15. Ann Neurol. 1994 35: 513-29.
16. Transfusion 1998 38:810-16.
17. Brown, P. Curr. Op. Hematol. 1995 2:472-77
18. Lancet 1997 350: 903-7.
19. Lancet 1997 350: 908-10.
20. FEMS Immunol. Med. Microbiol 1998 21:91-5.
21. Br. Med. J. 1996 315:389-95.
22. Lancet 1999 353:183-9.
23. Biologics 1992 20: 155-58.
24. Arch. Virol. 1994 139:313-26.
25. TSE Advisory Committee Transcripts, December 18, 1998: http://www.fda.gov/ohrms/dockets/ac/cber98t.htm
26. TSE Advisory Committee Transcripts, June 2-3, 1999: http://www.fda.gov/ohrms/dockets/ac/99mtbc.htm
27. http://www.ehs.ucsf.edu/manuals/BSM/appendix%20L.html